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| ANGELL, JON E | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1635 | 17 |

DATE MAILED: 09/10/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Applicati n No. | Applicant(s) | |
|---|---|---|---|
| | 09/887,527 | SIEMEISTER ET AL. | |
| | Examiner | Art Unit | |
| | J. Eric Angell | 1635 | |

*-- The MAILING DATE of this communication appears on the cover sheet with th correspondence address --*

**Period f r Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *24 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *8,12,14 and 17-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9-11,13,15 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 June 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

1. This Action is in response to the communication filed on 6/24/03, as Paper No. 16. Claims 1-22 are currently pending in the application and are addressed herein.

### *Election/Restrictions*

2. Applicant's election with traverse of Group I (claims 1-7 and 9-11), subgroup A interferes/inhibits VEGF/VEGFR (claims 1-7 and 9-11), subgroup (i) a small molecule, subgroup (a) SEQ ID NO: 60, and subgroup (b) ((4-chlorophenyl)[4-(4-pyridylmethyl)-phthalazine-1-yl]ammonium hydrogen succinate in Paper No. 16 is acknowledged. The traversal is on the ground(s) that examination of the full scope of the claims would not present a serious search burden for the Office. This is not found persuasive because, as set forth in a previous Office Action, the claims encompass compositions comprising patentably distinct molecules such as a monoclonal antibody, soluble polypeptides, small molecules, and antibody/peptide conjugates. All of these molecules have distinct classifications and additionally, the search for each molecule would require different search terms, demonstrating that the searched for each molecule are not coextensive—prima facie evidence of a serious search burden.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 8, 12, 14 and 17-22 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 16.

***Priority***

4. Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Europe on 6/23/2000. It is noted, however, that applicant has not filed a certified copy of the 00250194.8 application as required by 35 U.S.C. 119(b).

5. Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Europe on 6/28/2000. It is noted, however, that applicant has not filed a certified copy of the 00250214.4 application as required by 35 U.S.C. 119(b).

6. Since the certified copies of the above mentioned applications have not been received, Applicants do not receive the benefit of the filing date of the priority applications.

***Information Disclosure Statement***

7. The information disclosure statement (IDS) filed 11/21/02 contains a copy of an International Search Report (ISR) related to the instant application. However, the IDS does not contain form PTO-1449 listing the references referred to in the ISR. Furthermore, the submitted IDS fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. The IDS has been placed in the application file, and the ISR has been considered, but the information referred to therein has not been considered because copies of the references have not been provided. If Applicant's wish to have all of the references of the ISR fully considered, they are asked to submit a legible copy of each reference and form PTO-1449 listing all of the references which Applicants wish to have considered.

***Specification***

8. The disclosure is objected to because of the following informalities: the specification refers specifically to the peptide of SEQ ID NO: 34a (e.g., see p. 15, lines 23-25). However, it does not appear that SEQ ID NO: 34a is present in the paper sequence listing. It is believed that SEQ ID NO: 34a has been amended such it is now SEQ ID NO: 60; therefore, the appropriate change to all references to SEQ ID NO: 34a should be made in the specification.

Appropriate correction is required.

***Claim Rejections - 35 USC § 112, second paragraph***

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1-7, 9-11, 13, 14, 15 and 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

11. Claims 1-7 recite the phrase, "Pharmaceutical compositions comprising one or several agents as compound I... and comprising one or several agents as compound II..." This phrase renders the claims indefinite because it is unclear how several agents can comprise compound I or compound II because one of ordinary skill in the art would understand the term "compound" to be a one molecule (e.g., one molecule comprising more than one element chemically linked to form a single agent). For instance, the noun "compound" is defined in Webster's Collegiate Dictionary, Tenth Edition, as something formed by a union of elements or parts; esp : a distinct

substance formed by chemical union of two or more ingredients in definite proportion by weight." Therefore, it is unclear how a composition can comprise several agents as compound I and/or compound II.

12. Additionally, claims 1-7 are unclear because it is unclear if all "pharmaceutical compositions" encompassed by the claims comprise both compound I and compound II or if compound I and compound II are in different pharmaceutical compositions. Claims 9-11, 13, 14, 15 and 16 are dependent claims and are rejected for the same reasons.

13. Similarly, claims 10 is drawn to pharmaceutical compositions according to claim 1 which comprise as compound I at least one of: [compounds] (a)-(e). Again it is unclear how a compound (compound I) can comprise more than one compound as a compound must be a single chemical, as indicated above.

14. Claim 11 is drawn to "pharmaceutical compositions according to claim 1which comprise as compound II at least one of [compounds] (f)-(j). Again it is unclear how a compound (compound II) can comprise more than one compound as a compound must be a single chemical, as indicated above. Furthermore, it is unclear if compounds are missing from claim 11, because the claim only recites compounds starting with compounds (f) (i.e., f-j).

15. Claim 15 is drawn to "pharmaceutical compositions according to claim 1 which comprise as compound I and/or compound II at least one small molecule of general formula I". Again it is unclear how a compound (compound I or compound II) can comprise more than one small molecule, as a compound must be a single chemical, as indicated above.

To the extent the rejected claims can be generally interpreted in view of the specification, the following rejections are set forth.

***Claim Rejections - 35 USC § 112, first paragraph***

16. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

17. Claims 1-4, 6, 7, 9-11, 13, 15 and 16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

18. The instant claims are drawn to 1) compounds which can modulate the biological activity function of one or several VEGF/VEFG receptor systems and/or the biological function of one or several Angiopoietin/Tie receptor systems; and 2) molecules which can inhibit or interfere with the biological function of VEGF/VEGF-receptor **and** Angiopoietin/Tie-receptor systems. It is noted that the term "modulates" indicates that the compound has the ability to both increase and decrease the biological activity of one or several VEGF/VEGF-receptor or Angiopoietin/Tie-receptor systems.

The Written Description Guidelines for examination of patent applications indicates, "the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, or by disclosure of relevant, identifying characteristics, i.e. structure or other physical and/or other chemical properties, by functional characteristics coupled with a known or disclosed correlation between

function and structure, or by a combination of such identifying characteristics, sufficient to show applicant was in possession of the claimed genus." (See MPEP 2100-164)

Regarding compounds which can modulate the biological activity function of one or several VEGF/VEFG receptor systems and/or the biological function of one or several Angiopoietin/Tie receptor systems, the specification does not describe any molecules which have the ability to "modulate" (i.e., increase and decrease the biological activity) of any receptor system. The specification does disclose a number of molecules which can inhibit or interfere with the biological function of VEGF/VEGF-receptor systems, such as small molecules of general formula I, as well as a specific monoclonal antibody (mAB 4301-42-35), as well as the single chain antibody conjugates scFv-tTF and L19 scFv-tTF. Additionally, the specification has disclosed one molecule which ha been shown to inhibit/interfere with Angiopoietin/Tie-receptor systems, the sTie2 molecule. However, there is no description of any compounds which can both increase and decrease the biological function of the contemplated receptor systems. Molecules which can increase the biological function of the claimed receptor systems were known in the art, such as the ligands that binds to the receptors. However, the relevant art does not teach any molecules which have the ability to increase and decrease the biological function of the VEGF/VEGF-receptor and Angiopoietin/Tie-receptor systems. Furthermore, there is no disclosure in the specification which indicates the relevant identifying characteristics of any "modulator" molecules. There is no indication of any particular structures which would confer "modulator" activity to a molecule.

Therefore, the specification has not described a representative number of "modulator" molecules nor has the specification identified the relevant structural characteristics common to

the "modulator" molecules in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Regarding the molecules which can inhibit or interfere with the biological function of VEGF/VEGF-receptor **and** Angiopoietin/Tie-receptor systems, the specification does not disclose any molecules which can inhibit or interfere with **both** the VEGF/VEGF-receptor **and** the Angiopoietin/Tie-receptor system. The specification has described molecules which can inhibit/interfere with the biological function of **either** VEGF/VEGF-receptor systems (such as the small molecule of general formula I, mAB 4301-42-35, scFv-tTF and L19 scFv tTF) **or** the Angiopoietin/Tie-receptor systems (sTie2). Furthermore, the prior art does not teach any molecules which can inhibit/interfere with both VEGF systems and Angiopoietin systems. The specification does not identify any particular structures of the molecules which can interfere with both the VEGF and Angiopoietin systems.

Therefore, the specification has not described a representative number of molecules which can inhibit/interfere with the biological function of VEGF systems and Angiopoietin systems, nor has the specification (or prior art) identified the relevant structural characteristics common to the claimed molecules in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

19. Additionally, claims 1-4, 6, 7, 9-11, 13, 15 and 16 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement in view of the written

description rejection above. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

*Wands* states on page 1404,
"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

As mentioned above, the claims encompass pharmaceutical compositions comprising one or several agents which can modulate the biological function of the VEGF/VEGF-receptor and/or the Angiopoietin/Tie-receptor systems as well as molecules which can inhibit/interfere with the biological activity of both the VEGF systems and Angiopoietin systems. The claims encompass an indeterminate (but most likely huge) number of molecules considering every possible molecule encompassed by the claims, including molecules which have yet to be discovered. Considering that the prior art does not recognize any molecules which have the ability to both increase and decrease the biological function of the VEGF/VEGF-receptor and/or the Angiopoietin/Tie-receptor systems and that the specification does not disclose any working examples of the claimed molecules or even the basic structures of these molecules; additional experimentation would be required in order for one of skill in the art to be able to make and use the invention to the full scope encompassed by the claims. Considering that none of the

modulator molecules and none of the molecules which can interfere with both VEGF and Angiopoietin systems are known, and considering the basic structures of the molecules have not been disclosed, the amount of additional experimentation required to identify a representative number of each of these molecules is deemed to be undue.

20. Claims 2-7 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

21. The instant claims are drawn to compounds which are targeted to the endothelium. Claims 2, 4-7 encompass compounds which are targeted to the endothelium via the VEGF/VEGF-receptor and/or Angiopoietin/Tie-receptor systems.

22. The Written Description Guidelines for examination of patent applications indicates, "the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, or by disclosure of relevant, identifying characteristics, i.e. structure or other physical and/or other chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show applicant was in possession of the claimed genus." (See MPEP 2100-164)

23. In the instant case, the specification has only described a few molecules which are targeted to the endothelium. Specifically, the specification has identified a monoclonal antibody

(mAB 4301-42-35) and the single chain antibody conjugates scFv-tTF and L19 scFv-tTF as molecules which are targeted to the endothelium via the VEGF/VEGF-receptor system; and sTie2, which is targeted to the endothelium via the Angiopoietin/Tie-receptor system. The specification does not describe any other molecules which are targeted to the endothelium. Furthermore, the relevant art does not teach any other molecules which are targeted to the endothelium via VEGF/VEGF-receptor and/or Angiopoietin/Tie-receptor systems. Additionally, there is no disclosure in the specification which indicates the relevant identifying characteristics of any molecule which is targeted to the endothelium via the VEGF/Angiopoietin-Tie systems. There is no indication of any particular sequences or structures which would confer endothelium targeting activity to a molecule.

Therefore, the specification has not described a representative number of endothelium targeted molecules nor has the specification identified the relevant structural characteristics common to the endothelium targeting molecules in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

24. Additionally, claims 2-7 are also rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement in view of the written description rejection above. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

*Wands* states on page 1404,
"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

As mentioned above, the claims encompass pharmaceutical compositions comprising one or several endothelium targeting agents, and include molecules which are targeted to the endothelium via the VEGF/VEGF-receptor and/or the Angiopoietin/Tie-receptor systems. The claims encompass an indeterminate (but most likely huge) number of molecules considering every possible molecule encompassed by the claims, including molecules which have yet to be discovered. Considering that limited number of such molecules described in the specification and recognized in the prior art; additional experimentation would be required in order for one of skill in the art to be able to make and use the invention to the full scope encompassed by the claims. The amount of additional experimentation required to identify a representative number of molecules encompassed by the claims is deemed to be undue.

25. Claims 1-7, 9-11, 13, 15 and 16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A pharmaceutical composition comprising a molecule which interferes with or inhibits the biological function of the VEGF/VEGF-receptor system wherein said molecule is a small

molecule having the general structure set forth in general formula I (such as (4-chlorophenyl)[4-[4-pyridylmehtyl)-phthalazin-1-yl]ammonium hydrogen succinate);

does not reasonably provide enablement for the full scope of the claims. Specifically, the claims are not enabled for a pharmaceutical composition comprising a molecule that interferes with or inhibits the biological activity of the VEGF/VEGF-receptor system and/or the Angiopoietin/Tie-receptor system, wherein said molecule is SEQ ID NO: 60. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

*Wands* states on page 1404,
"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The instant claims are drawn to a pharmaceutical composition(s) comprising one or several agents as compound I which modulate the biological function of the VEGF/VEGF-receptor system and one or several agents as compound II which modulate the biological activity of the Angiopoietin/Tie-receptor system. Thus, the nature of the claims is pharmaceutical compositions which can modulate angiogenesis by modulating the biological function of the VEGF or angiopoietin systems. Additional claims are drawn to pharmaceutical compositions

comprising a molecule/molecules, which inhibit or interfere with the biological function of the VEGF/VEGF-receptor and/or Angiopoietin/Tie-receptor systems.

The lack of enablement with respect to molecules that (1)"modulate" biological function, (2) inhibit the biological function of both the VEGF and Angiopoietin systems, and (3) target the endothelium, is addressed above.

The breadth of the claims

The claims are very broad and encompass compositions comprising any molecule which can modulate the biological function of the VEGF and/or Angiopoietin systems. The elected molecules which must inhibit/interfere with the biological function of the VEGF and/or Angiopoietin systems are: the polypeptide of SEQ ID NO: 60 and the small molecule ((4-chlorophenyl)[4-(4-pyridylmehtyl)-phthalazin-1-yl]ammonium hydrogen succinate).

Working Examples and Guidance in the Specification

Regarding the enablement of the elected molecules, the specification has several examples which indicate the elected small molecule is an anti-angiogenic molecule which inhibits/interferes with the biological function of the VEGF system (e.g., see Examples 1, 4 and 6, starting at page 22 of the specification). The specification also indicates that ((4-chlorophenyl)[4-(4-pyridylmehtyl)-phthalazin-1-yl]ammonium hydrogen succinate) can work in combination with other anti-angiogenic factors that inhibit VEGF or Angiopoietin biological function (Examples 1, 4, 6).

However, the specification does not have any working examples indicating that the polypeptide set forth in SEQ ID NO: 60 has any anti-angiogenic activity, nor is their any evidence presented that the polypeptide of SEQ ID NO: 60 inhibits or interferes with the biological activity of the VEGF or Angiopoietin systems. In fact, the specification does not identify any specific function for the polypeptide of SEQ ID NO: 60. The only description of SEQ ID NO: 60 found in the specification is the amino acid sequence of SEQ ID NO: 60. There is no description of any particular function of SEQ ID NO: 60 described in the specification.

The unpredictability of the art and the state of the prior art

Looking to the relevant art for function of the polypeptide of SEQ ID NO: 60, it is noted that the closest polypeptide found is 99.1% identical to SEQ ID NO: 60 (see attached alignment). The sequence identified as being 99.1% identical to SEQ ID NO: 60 is CRIM1 (see attached). CRIM1 is described by Glienke et al. (Mechanisms of Development; 2002, 119(2) pages 165-175) as being expressed in blood vessels in vivo, and being involved in endothelial cell capillary formation in vitro by using antisense technology to inhibit CRIM1 expression, resulting in impaired capillary formation (see abstract). Specifically, Glienke teaches, "Taken together our results imply a possible role of CRIM1 in capillary formation and maintenance during angiogenesis." (See abstract).

Therefore, the closest art (post filing) indicates that a polypeptide 99.1% identical to SEQ ID NO: 60 has angiogenic properties, exactly the opposite function that the SEQ ID NO: 60 is required to have in order to inhibit/interfere with VEGF/VEGF-receptor and/or Angiopoietin/Tie receptor systems.

Quantity of Experimentation

Considering that the molecules encompassed as compound I and or compound II are required to inhibit/interfere with VEGF/VGF-receptor or Angiopoietin/Tie-receptor system biological functions (i.e., the molecule must be anti-angiogenic), and further considering that 1) Glienke teaches a polypeptide 99.1% identical to SEQ ID NO: 60 that has angiogenic properties, and 2) the instant specification does not disclose any working examples indicating the biological function of SEQ ID NO: 60; one of skill in the art would be required to perform additional experimentation in order to determine the biological function of SEQ ID NO: 60.

Level of the skill

The level of the skill required is deemed to be high, Ph.D. level.

Conclusion

Considering the nature of the invention, the breadth of the claims, the high degree of skill required, the lack of working examples and guidance in the specification (with respect to SEQ ID NO: 60 as an anti-angiogenic molecule), and the teachings in the art which indicate that a polypeptide 99.1% identical to SEQ ID NO: 60 has angiogenic activity, it is concluded that the amount of experimentation required to make and use the claimed invention is undue.

***Claim Rejections - 35 USC § 102***

26. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

27. Claims 1-7, 9-11, 15 and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Wood et al. (Cancer Research, 2000; Vol. 60, pages 2178-2189).

It is noted that the claims are rejected to the extent that they read on the enabled subject matter set forth above; namely, a pharmaceutical composition comprising as molecule I and molecule II, a molecule which interferes with or inhibits the biological function of the VEGF/VEGF-receptor system wherein said molecule is a small molecule having the general structure set forth in general formula I, including (4-chlorophenyl)[4-[4-pyridylmehtyl)-phthalazin-1-yl]ammonium hydrogen succinate).

It is noted that the specification discloses that (4-chlorophenyl)[4-[4-pyridylmehtyl)-phthalazin-1-yl]ammonium hydrogen succinate) is described by Wood et al. on page 22, line 19 of the specification.

Wood teaches a pharmaceutical composition comprising a molecule named PTK787/ZK 222584 (hereafter PTK787/ZK), also known as (1-[4-chloroanilino]-4-[pyridylmethyl] phthalazine succinate. Wood teaches that PTK787/ZK is "a potent inhibitor of vascular endothelial growth factor (VEGF) receptor tyrosine kinases, active in the submicromolar range." (See abstract). Furthermore, Wood teaches that a pharmaceutical composition comprising PTK787/ZK can inhibit tumor growth in vivo (see Table 2, page 2183).

28. Claims 1-7, 9-11, 15 and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Bold et al. (WO 98/35958).

It is noted that the claims are rejected to the extent that they read on the enabled subject matter set forth above; namely, a pharmaceutical composition comprising as molecule I and

molecule II, a molecule which interferes with or inhibits the biological function of the VEGF/VEGF-receptor system wherein said molecule is a small molecule having the general structure set forth in general formula I, including (4-chlorophenyl)[4-[4-pyridylmehtyl)-phthalazin-1-yl]ammonium hydrogen succinate).

Bold teaches the molecules having the general structure of general formula I. Bold teaches phthalazines that have anti-angiogenic activity and pharmaceutical compositions comprising the phthalazines (see abstract). Specifically, Bold teaches new phthalazine derivatives, processes for their preparation, and method of using the phthalazines (alone or in combination with other pharmaceutically active compounds) for treating humans or animals with proliferative diseases, such as cancer (see p. 1, first paragraph). Bold defines the phthalazine molecules as molecules having the general formula set forth in general formula I (beginning on page 3 of the specification). Furthermore, Bold specifically claims, "1-(4-chloroanilino)-4-(4-pyridylmethyl)phthalazine of formula I according to claim 1, or a pharmaceutically acceptable salt thereof." (See claim 7, page 104); and, "A pharmaceutical preparation, comprising a compound of formula I, according to any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof, or a hydrate or solvate thereof, and at least one pharmaceutically acceptable carrier." (See claim 10). Considering the specification indicates the elected small molecule was described by Wood et al. (see PTK787/ZK, above), it is clear that Bold teaches a pharmaceutical composition comprising the elected small molecule and all small molecules of general formula I.

***Conclusion***

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is (703) 605-1165. The examiner can normally be reached on M-F (8:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

DAVE T. NGUYEN
PRIMARY EXAMINER

J. Eric Angell
AU 1635